INCIDENCE OF LYMPH NODE METASTASES IN CLINICAL EARLY STAGE LOW GRADE MUCINOUS OVARIAN CARCINOMA

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Abstract

Background: The use of lymph node sampling during staging procedures in clinical early stage mucinous ovarian carcinoma (MOC) is an ongoing matter of debate. The incidence of lymph node metastases in MOC in relation to tumor grade is unknown. If lymph node metastases in clinical early stage G1 MOC would be non-existent, lymph node sampling might be safely omitted. We aimed to determine the incidence of lymph node metastases in clinical early stage MOC per tumor grade.

Materials & Methods: Histology report summaries from patients with MOC between 2002 and 2012 were obtained from the Dutch National Pathology Registry (PALGA). All reports were reviewed to confirm diagnosis, tumor grade and presence of lymph node metastases. Clinical data, surgery reports and radiology reports of patients with lymphadenopathy, were retrieved from hospital files.

Results: In the Netherlands, 915 patients with MOC were diagnosed and 426 underwent lymph node sampling. The other 489 patients had either cytoreductive surgery or were staged without lymph node sampling. In 7 patients, lymph node metastases were discovered by lymph node sampling. In 4 of 190 (2.1%) G1 MOC patients, lymph node metastases were present, compared to 1 of 115 (0.9%) G2 MOC patients and 3 of 22 (13.6%) G3 MOC patients. Tumor grade was not specified in 99 patients. No recurrence-free survival benefit from lymph node sampling was observed in patients with clinical early stage MOC.

Conclusion: These data indicate that lymph node sampling can be safely omitted in patients with G1 and G2 MOC without clinical suspicion of metastases.

Introduction

Epithelial ovarian cancer (EOC) is the cancer with the highest mortality of all gynecological malignancies. In the Netherlands, each year approximately 1300 patients are diagnosed with this disease. EOC is a term that encompasses serous, mucinous, seromucinous, endometrioid, clearcell and undifferentiated adenocarcinomas. The majority of patients with EOC are diagnosed with serous adenocarcinoma. Mucinous ovarian carcinoma (MOC) is a relatively rare subgroup of these ovarian malignancies. Due to revised criteria for the diagnosis of MOC, its incidence has even further declined over the past decades and is now estimated to be 3-5% of all EOC [1, 2].

Patients with MOC often present with a large unilateral ovarian mass without metastasized disease. In these patients, prognosis is relatively good with a 5-year disease free survival of 90.8% [3]. However, the course of advanced stage MOC is less favorable with fast progression and low response rates to chemotherapy. Seromucinous carcinoma is a rare ovarian malignancy that has been identified as a separate entity in the revised World Health Organization Classification of Tumors of the Female Reproductive Organs [4]. This tumor type is characterized by an admixture of serous, mucinous and endometrioid cell types. Moreover, patients with a seromucinous carcinoma are primarily diagnosed with disease confined to the ovary. Therefore, their prognosis is relatively good [5].

In patients with clinical early stage EOC, a complete staging procedure including lymph node sampling is recommended to exclude the presence of microscopic metastases. During the staging procedure, bilateral salpingo-oophorectomy, hysterectomy and (infracolic) omentectomy are performed and peritoneal biopsies are taken. Furthermore, a lymph node sampling of at least 10 lymph nodes from the para-aortic and pelvic region is advised. In many patients with MOC, this procedure is also performed; although, several studies have demonstrated a low incidence of lymph node metastases of 0.0-6.7% [6, 7].

Apart from histological classification, EOC can be divided by tumor grade. Internationally, the Silverberg/Shimizu criteria, by which the tumor is rated for dominating architectural pattern, nuclear atypia and mitotic activity rate, are often used. However, a two-tier system dividing the tumor into either low or high-grade tumors is preferred by more and more pathologists [8, 9]. These systems are primarily developed for serous and endometrioid carcinomas, but are less applicable to MOC because of their overall low-grade architectural appearance. No histological grading system has been universally accepted for MOC. As a result, most pathologists use the three-tier grading system for MOC, in the absence of a better alternative. Histological grading is important because of its prognostic relation, but can also influence the choice of treatment. In several histotypes of EOC, low-grade tumors have a more indolent course of disease with a favorable progression-free and overall survival, compared to high-grade tumors [10]. It can be expected that patients with low-grade tumors demonstrate a much lower incidence of lymph node metastases compared to high-grade tumors. Indeed, Kleppe *et al.* demonstrated that 4.0% of serous and endometrioid EOC patients with grade (G) 1 tumors and apparent FIGO stages I and II disease

had lymph node metastases, compared to 20.0% in G3 tumors. [6]. In MOC, the correlation between tumor grade and lymph node metastases is unknown. We hypothesized that lymph node metastases in clinical early stage G1 MOC have a low incidence or are non-existent. The aim of this study was to evaluate the need for a complete staging procedure, including lymph node sampling in patients with clinical early stage MOC of different tumor grades.

Materials and methods

Patient selection

The Dutch Pathology Registry (PALGA) [11], a nationwide network and registry that records all histopathology and cytopathology since 1991, was searched after approval of the privacy committee of PALGA. All patients diagnosed with MOC between January 2002 and December 2012 were selected based on pathology reports comprising the terms: “ovary” OR “tube”, AND “mucinous carcinoma” OR “mucinous adenocarcinoma” OR “mucin”. The pathology reports during treatment of MOC, as well as all reports before and after treatment with a follow-up period of at least 24 months, were obtained. A database of 18,465 pathology reports from a total of 1828 patients was built. For privacy reasons, all patients from the registry are itemized by a specific PALGA-code. Under this code, excerpts containing anonymized pathology reports, dates of tissue collection and age at time of tissue collection are registered. Researchers had no access to patient names or private information. Therefore, no patient informed consent and no additional approval of the Institutional Review Board was required.

All excerpts were initially scrutinized by the principal author (JVB). Ovarian tumors with a histological diagnosis other than MOC, tumors with insufficient criteria of invasive malignancy (i.e. borderline tumor, carcinoma *in situ*), ovarian metastasis of tumors from a different primary origin and reports with inconclusive data were excluded (for exclusion criteria, see Figure 1). In case of ambiguity concerning diagnosis, reports were discussed with an expert in gynecologic pathology (KVV). FIGO stage was determined for each tumor. Of each case, the primary diagnosis and official revision of histopathology were documented.

Seromucinous, endocervical-type mucinous and Müllerian mucinous carcinomas or mixed cell types with a mixed endometrioid or serous and mucinous aspect were collectively grouped as seromucinous carcinoma, according to the new WHO-guidelines [12].

Information including clinical data, surgery reports, radiology reports and follow-up data of all patients with lymph node metastases was retrieved from the hospital files via an intermediate procedure of PALGA. Anonymized clinical data and patient characteristics were requested from the treating physicians to maintain absolute privacy of the patient. No histology was required for this study. Therefore, no informed consent was needed to collect these additional clinical data.

Statistical analyses

The incidence rate of lymph node metastases in patients with MOC was calculated by dividing the

patients with metastases by the total number of patients. Additionally, to gain insight into changes in incidence of MOC over the study period, incidence rates per year and per 100,000 women were calculated with the average yearly female population numbers in the Netherlands [13]. Recurrence-free survival (RFS) was calculated for all patients that had recurrent disease, confirmed by histological examination. Normally distributed data was described as mean values with standard deviations. In case data was not normally distributed, median values and ranges (0-100%) were reported. Statistical analyses were performed using IBM SPSS (Statistical Package for the Social Sciences) version 22.0 (SPSS Inc., Chicago, Illinois). The two-sided Chi-square test was used for categorical variables and the student's t-test was used to evaluate differences in normally distributed, continuous variables. Kaplan-Meier survival curves were generated for FIGO stage I patients with and without lymph node sampling to determine RFS. Patients that were lost to follow-up, were right-censored in the survival curves. Equality of RFS between these groups was calculated with Log Rank (Mantel-Cox) tests.

Results

Mucinous ovarian cancer

From a search of PALGA, the Dutch Pathology Registry, a total of 1828 patients with possible MOC were identified between January 2002 and December 2012. After detailed examination of the reports from the PALGA registry, 803 patients were excluded for reasons such as ovarian metastases of a different primary origin or lack of malignancy, leaving 1025 patients eligible for our study (Figure 1). Of these 1025, patients diagnosed with a primary MOC totalled 915 individuals and 110 patients with a seromucinous carcinoma. Clinical characteristics of these patients with MOC are shown in Table 1.

The majority of patients were diagnosed with a G1 or G2 MOC. In the total group of patients with MOC, 17 (1.9%) patients were diagnosed with lymph node metastases. In 9 patients with nodal disease, lymph node metastases were removed during cytoreductive surgery for advanced disease or after histological biopsy of an enlarged lymph node. A significantly lower incidence of lymph node metastases was seen in G1 MOC (1.4%) compared to G3 MOC (5.7%, $p = 0.03$). No significant difference was seen between G1 and G2 MOC (1.4% vs. 2.6%, $p = 0.35$), or between G2 and G3 MOC ($p = 0.19$) (Table 1). During the 11 years included in this study, the incidence rates of MOC per 100,000 Dutch women per year declined (Figure 2).

To understand whether tumor grade influences the chance of lymph node metastases in clinical early stage MOC, we focussed on the patients who received staging procedures (Table 2). Complete staging procedures including lymph node sampling, were performed in 426 patients, revealing 8 patients with lymph nodes metastases. Patients with G1 and G2 disease showed significantly less lymph node metastases compared to G3 MOC (G1 versus G3 $p = 0.03$; G2 versus G3 $p = 0.01$). These data indicate that lymph node metastases in clinical early stage MOC of G1 and G2 disease are rare.

To examine whether the patients with lymph node metastases (n=8) had apparent evidence of lymphadenopathy on preoperative radiological imaging or during the staging procedures, we examined the clinical data of these patients (Table 3). Interestingly, in 5 out of 8 (62.3%) of patients with metastases identified during staging lymph node sampling, enlarged lymph nodes were already present on radiological examination or enlarged by palpation during the staging procedures. Thus, in patients with G1 MOC without clinical suspicion of metastatic disease, only 2 (95%CI 0.13-3.75%) patients had unexpected lymph node metastases. Patients with G2 MOC without signs of clinical metastases had no lymph node metastases found with staging procedures (95%CI 0-0.03%). However, 4.5% (95%CI 0.12-22.84%) of patients with G3 MOC, without pre-operative evidence of metastatic disease in the lymph nodes were shown to have (microscopic) lymphadenopathy.

Next, to evaluate whether tumor grade is correlated with RFS, Kaplan-Meier survival analyses were performed of all FIGO stage I patients with MOC (Figure 3a). A more favorable RFS was observed for patients with G1 and G2 MOC than for those with G3 MOC ($p < 0.0001$).

In 6.6% of patients with G1 MOC with FIGO stage I, recurrent disease was diagnosed after a median of 16 months (range 5-39), whereas 11.0% of patients with G2 MOC and 33.3% of patients with G3 developed recurrent disease after 15.5 and 8.0 months, respectively. RFS of clinical FIGO stage I patients without lymph node sampling and patients who underwent staging lymph node sampling were comparable for G1, G2 and G3 (Figure 3b). Table 3 demonstrates numbers of patients with recurrent disease and RFS per tumor grade. Taken together, these results demonstrate that performing lymph node sampling in the absence of clinical evidence of metastases does not favor RFS.

Seromucinous ovarian cancer

Of the 1828 patients who presented with EOC between January 2002 and December 2012, 110 patients were diagnosed with a seromucinous (or endocervical-type mucinous) carcinoma (Figure 1). During this time, the incidence of seromucinous carcinoma was stable (Figure 2). The characteristics of these patients are presented in Table 4. The mean age of this cohort was 56.1 years and there was no difference in age when the group was subdivided by grade. Most patients (58.3%) were diagnosed with G1 disease. Among the entire seromucinous carcinoma cohort, 5 (4.5%) patients had lymph node metastases. Strikingly, none of these lymph node metastases were found in patients with G1 seromucinous carcinoma. In 3 (60%) patients with lymphadenopathy, axillar or supraclavicular lymph node metastases were found, which was not found in the MOC patients. Staging procedures were performed in 46 out of 110 patients, but did not reveal any additional lymph node metastases. Recurrent disease occurred in 25 patients (22.7%) with seromucinous carcinoma. In patients with FIGO stage I disease with G1, G2 and G3 seromucinous tumors, recurrent disease occurred in 4 (12.9%), 3 (16.7%) and 2 (50%) patients, respectively. In conclusion, lymph node metastases in G1 seromucinous carcinoma could not be

found. However, the number of patients that received lymph node samplings in the present study is too small to draw solid conclusions from these results.

Discussion

The current study shows that the incidence of lymph node metastases in patients with clinical early stage G1 or G2 MOC is very low. In case of absence of enlarged lymph nodes on radiological examination or on palpation during staging procedures, only 0.7% of the patients with G1 and G2 MOC together had lymph node metastases. In addition, no RFS benefit from lymph node sampling was observed in patients with clinical FIGO stage I MOC.

This is the first study that reports lymph node metastases in MOC per tumor grade. Previous studies demonstrated a low overall incidence of lymph node metastases in clinical early stage MOC (0.0-6.7%) [6, 7]. Our study demonstrates that G3 MOC is associated with a higher incidence of lymph node metastases discovered during staging procedures, compared to G1 and G2 MOC. Staging lymph node samplings were performed in only 22 patients with G3 MOC. However, our findings suggests that G3 MOC has another clinical behavior leading to a more advanced stage disease at presentation and a higher incidence of lymph node metastases. Patients with G1 and G2 MOC presented with a similar course of disease, with equal FIGO stages at diagnosis, equal incidences of lymph node metastases and comparable RFS. This tumor grade specific behavior can also be seen in other histotypes of EOC, such as low grade and high grade serous carcinoma [14, 15]. Therefore, different tumor grades of MOC should not be regarded as one group, as G1 and G2 MOC represent a different course of disease than G3 MOC. The differences in clinical behavior may be explained by differences in genetic drivers. Several mutated genes have been identified for MOC, including KRAS, BRAF, CDKN2A and TP53 genes [16-19]. Recently, a study of Ryland *et al.* investigated the variances of the genomic landscapes between the tumor grades of MOC [16]. However, in this study, demonstrating evident differences between the tumor grades was hindered by the heterogeneity of MOC and the small study populations.

Defining tumor grade in MOC remains a matter of debate amongst pathologists, as the current classification system is suboptimal for MOC and a specific grading system does not exist. A new classification system of grading MOC is needed to optimize separating patients with poor prognosis from patients with more favorable prognosis. Our results implicate that possibly a two-tier classification system should be developed in which G1, G2 and G3 MOC are subdivided into a low grade and a high grade group. Identification of the molecular differences between tumor grades of MOC will also create a valuable contribution to the distinction of the different prognostic groups.

Lymph node sampling in early stage EOC has been the subject of debate for the past years. Previously, some studies demonstrated a survival benefit for patients with early stage EOC who received complete staging procedures [19, 20]. However, in these studies, different histotypes of EOC are taken together and none of these studies investigated MOC with focus on its separate

tumor grades. In The Netherlands, clear guidelines are formulated concerning staging procedures for clinical early stage EOC. Herein, a complete staging procedure is recommended with dissection of a minimum of 10 lymph nodes. In our study, only 64% of the patients with clinically early stage disease had a staging procedure with lymph node sampling. This number reflects the ongoing ambiguity amongst gynecologists concerning the necessity to perform a lymph node sampling in this group of patients.

In the current literature, only few studies with small numbers of included patients have investigated the behavior and morphology of the seromucinous carcinoma [20-22]. This is the first study reporting data of a large cohort with a total of 110 seromucinous carcinomas. This relatively uncommon EOC tends to behave different in comparison to MOC. Lymph node metastases were more common than in MOC, but did not occur in G1 seromucinous carcinoma. Also, in 60% of the patients with lymph node metastases, tumor involvement of axillary or supraclavicular lymph nodes was seen, which did not occur in the MOC group. Extraperitoneal lymph node metastases of high grade serous carcinoma at time of presentation has been described in the literature [23]. This suggests that G2 and G3 seromucinous carcinomas resemble a metastases pattern similar to that of a high-grade serous carcinoma. Future studies must be performed to demonstrate possible similarities in genetic drivers of these tumors. Interestingly, patients with a seromucinous carcinoma had no lymph node metastases found with staging lymph node sampling. However, the number of patients that received a lymph node sampling during staging procedures was small. Therefore, no robust conclusions can be drawn for these patients with a clinical early stage seromucinous carcinoma. These findings may be the basis for future studies in which multicentre collaboration is particularly needed to achieve sufficient study populations. For all tumor grades, recurrent disease appeared to occur more frequently in FIGO stage I patients with a seromucinous carcinoma than patients with MOC (G1 12.9%, G2 16.7%, G3 50.0%). These results are consistent with the new WHO Classification of Tumors of the Female Reproductive Organs of 2014 [12], in which seromucinous carcinomas are included as a separate entity, rather than as a variant of MOC.

A limitation of our study is that the incidence of recurrent disease was based on histopathological examination. This might have led to an underestimation of the incidences of recurrences. An obvious recurrence diagnosed with clinical or radiological examination might, in some cases, have been treated without histopathological confirmation.

A second limitation is that small sized, non-suspicious lymph nodes can still contain microscopic metastatic disease. The chance of not finding small lesions is higher in the patients without lymph node sampling. In our study, the number of removed lymph nodes was unknown for 39.0% of patients who received lymph node samplings. In 39.2% of all staged patients, a minimum of 10 lymph nodes was resected, which number is supposed to reflect the lymph node status accurately in FIGO stage I patients [24, 25]. However, RFS was equal for both the groups with and without lymph node sampling. The differences between the grades of MOC are unlikely to change

because of this.

We based our results on existing pathology and radiology reports and no additional revision was performed to confirm diagnosis and absence of lymphadenopathy. Yet, our results showed that in 34.9% of all cases, official histopathological revision had already been performed. Furthermore, patients with MOC are treated in a third-line institute, where histopathological revision by an expert in gynecologic pathology is part of the standard care. However, in 24.3% of all diagnosed MOC, tumor grade was not specified in the pathology reports by pathologists. Our results emphasize the importance of a precise histopathological designation in combination with specification of tumor grade and should therefore be performed by a gynaecological oriented pathologist.

Unfortunately, we had no information concerning the administration of adjuvant chemotherapy. Although for G3 MOC or for non-optimally staged patients, administration of adjuvant chemotherapy may have been considered, it is unlikely that completely staged patients with FIGO stage I with G1 or G2 MOC have received chemotherapy. In addition, the poor chemosensitivity of MOC [26, 27] implicates that administration of adjuvant systemic treatment may have only minimal effect on the outcome of FIGO stage I MOC.

In conclusion, our results imply that staging lymph node sampling can be safely omitted in G1 and G2 MOC. Omitting this procedure could have a positive effect on surgery-related complications, total blood loss and operating time [28]. However, a well-trained and experienced surgeon is a prerequisite for the optimal assessment of enlarged lymph nodes during surgery and the subsequent decision whether lymph node sampling should be performed or not.

Figure 1. Flow chart of patient selection. NEED MORE DESCRIPTION OF WHAT YOU DID HERE

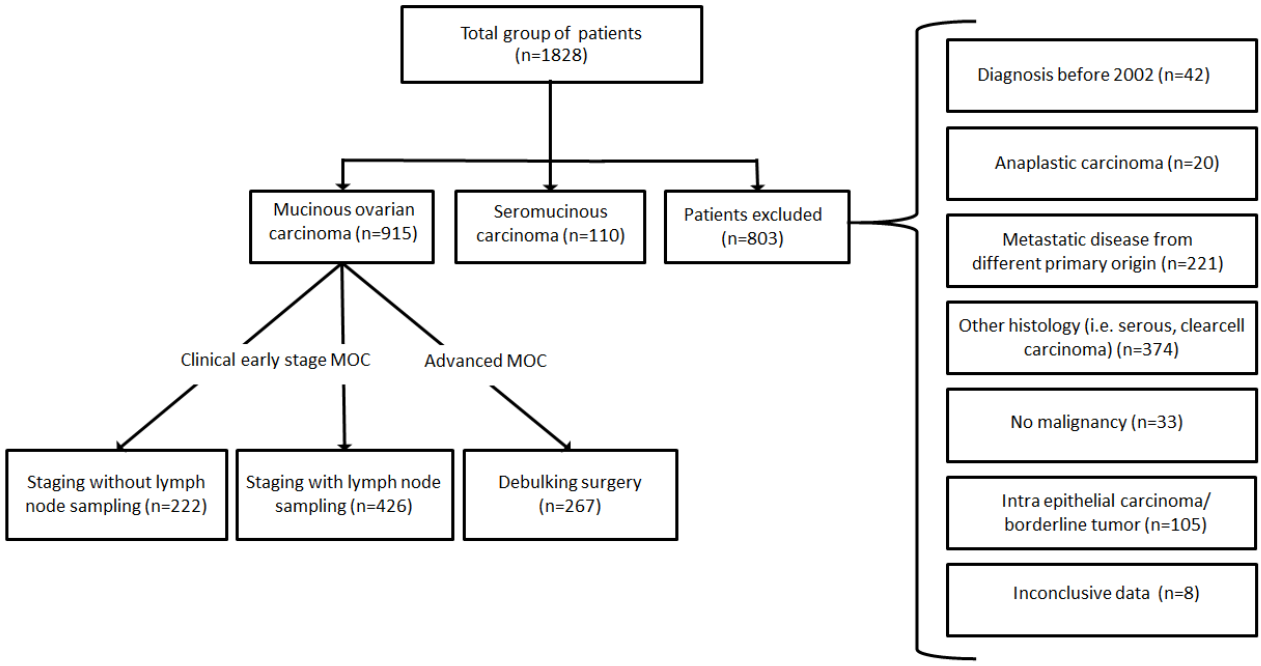


Figure 2. Incidence of mucinous and seromucinous ovarian cancer in The Netherlands between January 2002 and December 2012.

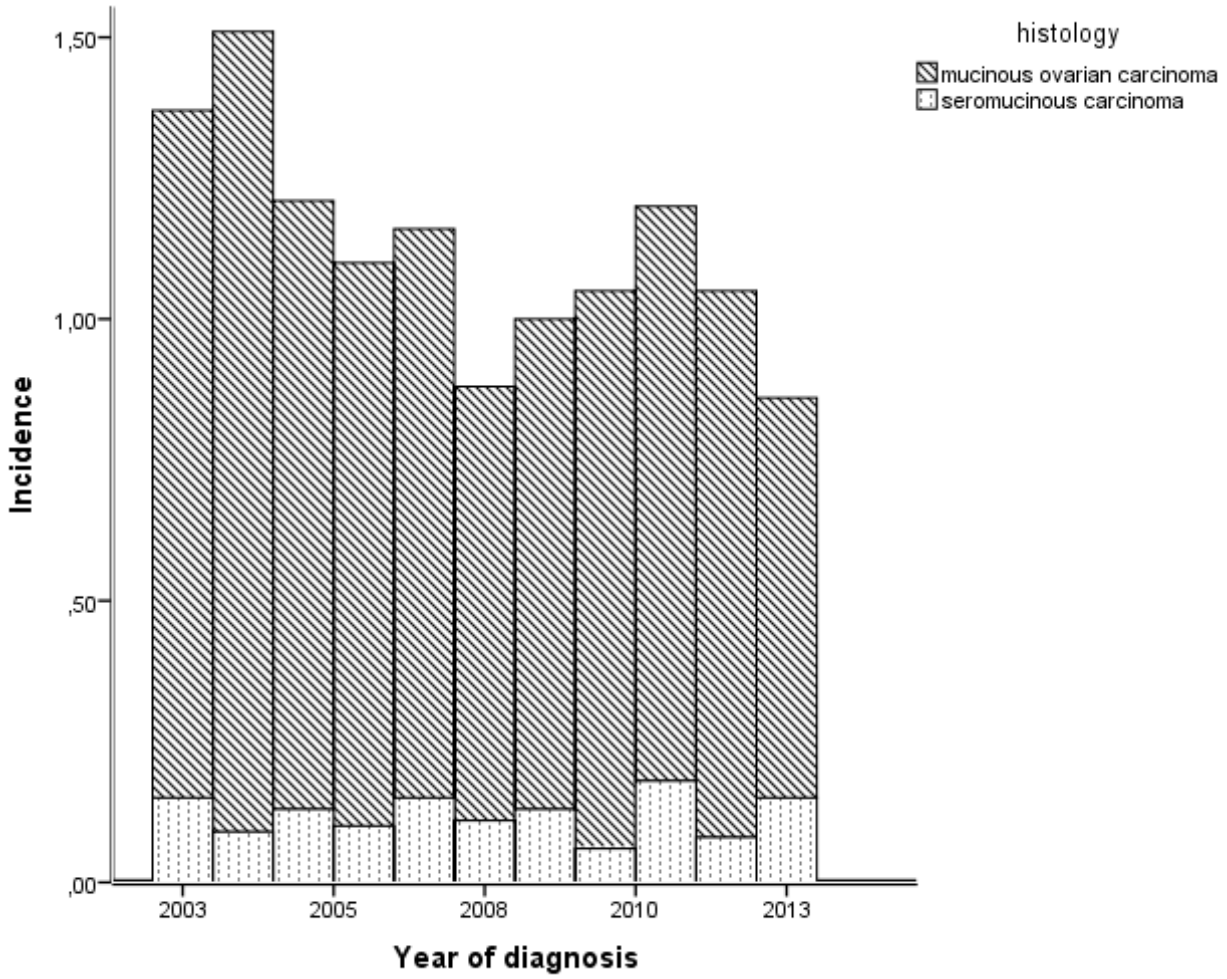


Table 1. Characteristics of total group of 915 patients with MOC per tumor grade.

Variable	All MOC					
		G1 MOC	G2 MOC	G3 MOC	Grade unspecified	*P*-value
***n* (%)**	915 (100)	369 (40.3)	229 (25.0)	88 (9.6)	229 (25.0)	
Mean age (yrs (95%CI))	55.7 (54.7-56.7)	54.0 (52.4-55.6)	55.4 (53.4-57.5)	56.8 (53.6-60.0)	58.1 (56.1-60.0)	0.02[a]
FIGO stage (n (%))						
I	623	286 (77.5)	162 (70.7)	26 (29.5)	149 (65.1)	
II	46	17 (4.6)	8 (3.5)	14 (15.9)	7 (3.1)	0.04[b]
III	159	42 (11.4)	41 (17.9)	32 (36.4)	44 (19.2)	
IV	29	4 (1.1)	8 (3.5)	9 (10.2)	8 (3.5)	
Unknown	58	20 (5.4)	10 (4.4)	7 (8.0)	21 (9.2)	
Histopathological revision (n (%))	319 (34.9)	151 (40.9)	75 (32.8)	30 (34.1)	63 (27.5)	0.01[c]
Tumor characteristics (n (%))						
Intestinal type	84 (9.2)	38 (10.3)	20 (8.7)	4 (4.5)	22 (9.6)	0.40[c]
Infiltrative growth	6 (0.7)	3 (0.8)	1 (0.4)	0 (0)	2 (0.9)	
Expansive growth	42 (4.6)	15 (4.1)	8 (3.5)	4 (4.5)	15 (6.6)	0.09[b]
LNM (n (%))						
Yes	17 (1.9)	5 (1.4)	6 (2.6)	5 (5.7)	1 (0.4)	<0.001[c]
No	428 (46.8)	188 (50.9)	117 (51.1)	21 (23.9)	102 (44.5)	
Unknown	470 (51.4)	176 (47.7)	106 (46.3)	62 (70.5)	126 (55.0)	

[a]One-Way ANOVA test
[b]Linear-by-Linear Association test
[c]Pearson Chi-Square test
LNM = Lymph node metastases

Table 2. Staging lymph node sampling performed in 426 patients with clinical early stage MOC per tumor grade.

Variable	G1 MOC n (%)	G2 MOC n (%)	G3 MOC n (%)	MOC Grade unspecified n (%)
Number of patients	190 (44.6)	115 (27.0)	22 (5.3)	99 (23.2)
LNM	4 (2.1)	1 (0.9)	3 (13.6)	0
Radiological examination in patients with LNM				
Patients with normal lymph nodes	3 (75)	0	2 (66.7)	-
Patients with enlarged lymph nodes	0	1 (100)	0	
Unknown	1 (25)	0	1 (33.3)	
Observations during surgery in patients with LNM				-
Patients with normal lymph nodes	2 (50)	1 (100)	1 (33.3)	
Patients with enlarged lymph nodes	2 (50)	0	2 (66.7)	

LNM = Lymph node metastases

Table 3. Differences between FIGO stage I patients with complete staging procedure and incomplete staging

Variable	FIGO stage I with complete staging* n=401	Clinical FIGO stage I incomplete staging** n=222	*P*-value
Tumor grade (n (%))			
G1	178 (44.4)	108 (48.6)	
G2	112 (27.9)	50 (22.5)	
G3	15 (3.7)	11 (5.0)	
Grade unspecified	96 (23.9)	53 (23.9)	
Recurrent disease (n (%))			
G1	9 (5.1)	10 (9.3)	0.22[a]
G2	11 (9.8)	4 (8.0)	0.48[a]
G3	5 (33.3)	5 (36.4)	0.60[a]
Grade unspecified	8 (8.3)	6 (11.3)	0.37[a]
Median RFS in months (range)			
G1	21.0 (5-39)	27.0 (19-146)	0.35[b]
G2	14.0 (5-46)	11.5 (9-46)	0.89[b]
G3	8.0 (6-24)	21.5 (7-107)	0.79[b]
Grade unspecified	14.0 (4-51)	17.0 (9-68)	0.39[b]

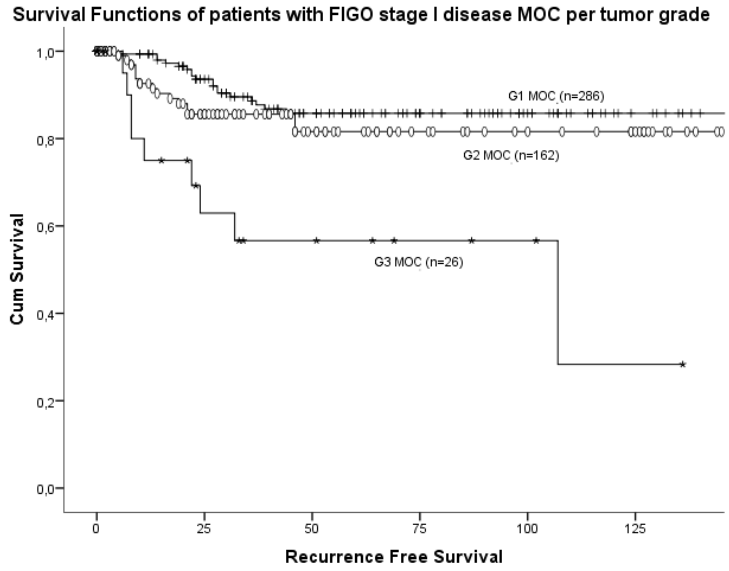
*Staging procedure including lymph node sampling with tumor-negative lymph nodes
**Staging procedure without lymph node sampling
LNM = Lymph node metastases
RFS = Recurrence free survival
[a]One-sided Fisher's Exact Test
[b]Log Rank Mantel Cox Test

Table 4. Characteristics of 110 patients with seromucinous ovarian carcinoma per tumor grade

Variable	All Seromucinous carcinoma					
		Seromucinous carcinoma G1	Seromucinous carcinoma G2	Seromucinous carcinoma G3	Seromucinous carcinoma Grade unspecified	P-value
n (%)	110 (100)	43 (39.1)	30 (27.3)	16 (14.5)	21 (19.1)	
Mean age (yrs (95%CI))	56.1 (53.5-58.8)	58.3 (54.0-62.5)	58.3 (53.4-63.1)	51.6 (43.6-59.6)	52.1 (45.4-58.7)	0.17[a]
FIGO stage (n (%))						
I	66 (60.0)	31 (72.1)	18 (60.0)	4 (25.0)	13 (61.9)	
II	13 (11.8)	4 (9.3)	5 (16.7)	2 (12.5)	2 (9.5)	0.56[b]
III	21 (19.1)	4 (9.3)	5 (16.7)	7 (43.8)	5 (23.8)	
IV	7 (6.4)	2 (4.7)	2 (6.7)	3 (18.8)	0 (0)	
Unknown	3 (2.7)	2 (4.7)	0 (0)	0 (0)	1 (4.8)	
Histopathological revision (n (%))	38 (34.5)	21 (48.8)	8 (26.7)	4 (25.0)	5 (23.8)	0.09[c]
LNM (n (%))						
Yes	5 (4.5)	0 (0)	2 (6.7)	2 (12.5)	1 (4.8)	0.10[c]
No	48 (43.6)	20 (46.5)	16 (53.3)	4 (25.0)	8 (38.1)	
Unknown	57 (51.8)	23 (53.5)	12 (40.0)	10 (62.5)	12 (57.1)	
Staging lymph node sampling (n (%))	46 (41.8)	19 (44.2)	16 (53.3)	3 (18.8)	8 (38.1)	
Recurrent disease (n (%))	25 (22.7)	7 (16.3)	9 (30.0)	4 (25.0)	5 (23.8)	0.58[c]

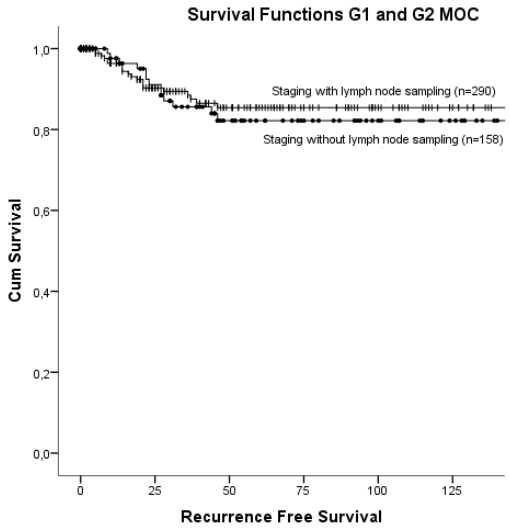
[a]One-Way ANOVA test
[b]Linear-by-Linear Association test
[c]Pearson Chi-Square test

Figure 4a. Kaplan Meijer curves of survival of all FIGO stage I patients with MOC per tumor grade.



Survival curves of all patients with clinically FIGO stage I MOC, with a favorable RFS for G1 MOC and a poorer RFS for G3 MOC (Log Rank 18.30, $p < 0.0001$).

Figure 4b. Kaplan Meijer curves demonstrating RFS of patients with FIGO stage I disease, G1 and G2 MOC, with and without lymph node sampling.



Survival curves are demonstrated of patients with G1 and G2 combined, who received staging procedures either with or without lymph node sampling. No survival benefit was observed in the patients who had lymph node sampling (Log Rank 0.183, $p = 0.67$).

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